Pitfalls in the diagnostic evaluation of subacute combined degeneration

Ulrich, A ; Müller, D ; Linnebank, M ; Tarnutzer, A A

Abstract: We report a case of a 43-year-old man presenting with a 2-week history of painless ascending sensory disturbances, suspected to be suffering from acute inflammatory polyneuropathy. On clinical examination, deep tendon reflexes were preserved and muscle strength was 5/5 everywhere. Gait was ataxic with positive Romberg test. Lumbar puncture was normal and electroneurography demonstrated demyelination. With spinal cord involvement centred on the posterior tracts on MRI, differential diagnosis focused on cobalamin deficiency. Initial laboratory work up showed nearly normal holotranscobalamin (43 pmol/L, normal>50) suggesting no vitamin B12 deficiency. Surprisingly, further testing including methylmalonic acid (3732 nmol/L, normal<271) and homocysteine (48.5 µmol/L, normal<10) showed an impairment of vitamin B12-dependent metabolism leading to the diagnosis of subacute combined degeneration. Only after repeated history taking did the patient remember having taken tablets containing cobalamin for 3 days before hospitalisation. In case of B12 deficiency, holotranscobalamin can rapidly normalise during supplementation, whereas methylmalonic acid and homocysteine might help to detect B12 deficiency in patients who recently started supplementation.

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TITLE OF CASE

Pitfalls in the diagnostic evaluation of subacute combined degeneration

Ulrich A (1), Müller D (2), Linnebank M (1), Tarnutzer AA (1)

(1) Department of Neurology, University Hospital Zurich, Zurich, Switzerland
(2) Institute of Clinical Chemistry, University Hospital Zurich, Zurich, Switzerland

SUMMARY

We report on a 43-year-old patient presenting with a two-week history of painless ascending sensory disturbances suspected to suffer from acute inflammatory polyneuropathy. On clinical examination, deep tendon reflexes were preserved and muscle strength was 5/5 everywhere. Gait was ataxic with positive Romberg test. Lumbar puncture was normal and electroneurography demonstrated demyelination. With spinal-cord involvement centred on the posterior tracts on MRI, differential diagnosis focused on cobalamin-deficiency. Initial laboratory work-up showed nearly normal holotranscobalamin (43pmol/l, normal>50) not suggesting vitamin B12-deficiency. Surprisingly, further testing including methylmalonic acid (3732nmol/l, normal<271) and homocysteine (48.5umol/l, normal<10) proofed an impairment of vitamin-B12-dependent metabolisms leading to the diagnosis of subacute combined degeneration. Only after repeated history taking, the patient remembered having taken tablets containing cobalamin for three days before hospitalization. In case of B12-deficiency, holotranscobalamin can rapidly normalize during supplementation, whereas methylmalonic acid and homocysteine might help to detect B12-deficiency in patients who started supplementation recently.

BACKGROUND

Acute ascending sensory deficits constitute a neurological emergency and require a thorough clinical evaluation and diagnostic work-up. The differential diagnosis of this clinical picture is broad and some underlying disorders require close monitoring and immediate treatment. This is especially true for acute inflammatory demyelinating polyneuropathy as it may rapidly progress and lead to respiratory failure and severe autonomic disturbances [1]. This disorder needs to be distinguished from other potential causes of ascending sensory deficits including toxic and malnutrition-related neuropathies and transverse myelopathy. Polyneuropathy due to cobalamin (vitamin-B12) deficiency, which can be attended by spinal cord and brain demyelination, is treatable by vitamin B12 substitution and is potentially reversible when treated early [2].
In the case presented here we lead through the diagnostic work-up for acute ascending sensory deficits and discuss potential pitfalls in the laboratory diagnostics of vitamin B12 deficiency.

CASE PRESENTATION

A 43-year-old male presented with a two-week history of painless ascending sensory disturbances affecting legs and arms. The patient had no cognitive complaints or visual disturbances. On initial history taking no toxic exposure or drug intake was reported (especially no use of acid-suppressing medication). The patient stated frequent consumption of meat products. The patient had no history of gastric surgery. Family history for neurological disorders was negative. On clinical examination, impaired touch and pain sensation (reaching up to the elbows and knees) was reported, and position sense and vibration sense were strongly reduced at the feet. There was also impaired sensation for touch below dermatome Th7 bilaterally. Deep tendon reflexes (including the Achilles tendon reflex) were weak but symmetric. Babinski sign was negative and muscle tone was normal. Muscle strength was 5/5 everywhere. Romberg showed increased sway, and gait was broad-based/ataxic. Cranial nerves were normal; no cerebellar deficits were noted. Later during hospitalization we learned about intramuscular B12-substitution two years before hospitalisation due to vitamin B12 deficiency without clinical symptoms detected in a routine screening as part of a health check-up (serum-B12 level May 2012: 120 pmol/l, normal: >180).

INVESTIGATIONS

Lumbar puncture was normal (including normal cell count, glucose, lactate and negative syphilis serology) except for slightly elevated total protein (0.56g/l, normal<0.5). Electroneurography showed increased distal motor latencies and reduced nerve conduction velocities and slightly increased F-wave latencies at the legs (Table 1), while electromyography was normal. Noteworthy, except for moderately reduced amplitude of the compound muscle action potential of the median nerve, no axonal changes were noted. These findings were consistent with sensorimotor demyelinating polyneuropathy of the legs.

Table 1: electroneurographic (ENG) findings (6 days after symptom onset):

Nerve	Motor nerve conduction velocity (m/s)	Distal motor latency (ms)	Temporal dispersion	F-latency (ms)	Sensory nerve conduction velocity (m/s)	cMAP (mV) / sNAP (µV)
L median N	distal 50 (n>48) proximal 62 (n>48)	4.1 (n<4.0)	none	29.4 (n<31)	distal 52 (n>49) proximal 51 (n>52)	3.0 / 20.6
R median N	distal 46 (n>48) proximal 65 (n>48)	4.2 (n<4.0)	none	NA	distal 56 (n>49) proximal 50 (n>52)	7.7 / 23.0
L ulnar N	NA	3.0 (n<3.2)	none	29.0 (n<32)	distal 50 (n>41) proximal NA	8.7 / 22.9
R ulnar N	distal 53 (n>44) proximal 69 (n>45)	2.5 (n<3.2)	none	29.9 (n<32)	distal 48 (n>41) proximal 61 (n>46)	7.9 / 19.6
L peroneal N	distal 38 (n>42) proximal 59 (n>41)	5.8 (n<4.9)	none	59.9 (n<56)	NA	5.6 (n>2.6 mV) / NA
R peroneal N	distal 26 (n>42) proximal 46 (n>41)	5.2 (n<4.9)	none	66.7 (n<56)	NA	4.1 (n>2.6 mV) / NA
L tibial N	29 (n>40)	4.8 (n<5.5)	none	65.5 (n<58)	NA	12.6 (n>5.8 mV) / NA
R tibial N	19 (n>40)	5.1 (n<5.5)	none	71.1 (n<58)	NA	8.7 (n>5.8 mV) / NA
L sural N (orthodrome, needle ENG)	NA	NA	NA	NA	38 (n>48)	NA / 12.3
R sural N (orthodrome, needle ENG)	NA	NA	NA	NA	40 (n>48)	NA / 19.5

Abbreviations: NA = not available

With normal median and ulnar nerve measurements, the upper extremity sensory deficits remained unexplained. We therefore obtained spinal cord imaging, demonstrating non-enhancing T2-hyperintensities (Fig 1AB) on the posterior columns (C2 to C5), which is characteristic of subacute combined degeneration. Cerebral MRI showed no abnormalities and neuropsychological testing demonstrated no cognitive deficits. Differential diagnosis now focused on cobalamin deficiency. However, initial laboratory work-up showed almost normal holotranscobalamin (43pmol/l, normal>50) levels not typical for clinically relevant vitamin B12 deficiency. Surprisingly, further laboratory testing demonstrated strongly increased methylmalonic acid (=MMA; 3732nmol/l, normal<271) and plasma total homocysteine (48.5umol/l, normal<10) levels proofing an impairment of vitamin B12-dependend metabolisms. Folate, zinc and copper levels were normal. These findings supported the diagnosis of cobalamin-associated subacute combined degeneration and peripheral polyneuropathy. Only after repeated history taking, the patient remembered having taken cobalamin-containing tablets for three days before hospitalization. We additionally analysed total cobalamin (133ng/l, normal range=180-914) from the initial blood sample, also showing only a moderately reduced level.

During the course of hospitalization, the patient developed shortness of breath and chest pain. With underlying pulmonary embolism confirmed by chest CT, he was started on rivaroxaban.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis was driven by the initial presentation of ascending sensory disturbances

and demyelinating neuropathy, while deep tendon reflexes were preserved and lumbar puncture was normal except for slightly elevated total protein levels. This combination made acute inflammatory demyelinating polyneuropathy unlikely and re-enforced a diagnostic work-up. In view of myelopathy, ischemia, metabolic-toxic causes and malnutrition/malabsorption were considered. With very high MMA and homocysteine levels, cobalamin deficiency became the most likely cause despite almost normal holotranscobalamin levels. Low iron serum levels supported the hypothesis of malnutrition/malabsorption. The supplementation of cobalamin a few days before hospitalisation explains why holotranscobalamin and total cobalamin levels were only slightly decreased on admission.

TREATMENT

Treatment with subcutaneous cyanocobalamin (1000 mcg) given every other day was initiated (intramuscular application was contraindicated due to pulmonary embolism treated with therapeutic heparin). Folic acid was supplemented as well.

OUTCOME AND FOLLOW-UP

Under treatment with cyanocobalamin, MMA and homocysteine levels continuously decreased, and were normal again after one month (Fig 2). Clinically, the patient reported significant improvement of sensory disturbances and gait ataxia. Follow-up MRI after two months showed significant regression of the dorsal column hyperintensities (Fig. 1CD). Upper gastrointestinal endoscopy revealed several duodenal ulcera, while no helicobacter pylori was found on biopsy, and anti-intrinsic factor and anti-parietal cell antibodies were negative. To which extent these duodenal ulcera reduced cobalamin absorption remains unclear. The patient is now under oral cobalamin and folic acid supplementation and received a proton pump inhibition treatment for six weeks. On follow-up examination four months after symptom onset sensory disturbances were greatly reduced with slight residual deficits in touch and pain sensation at the feet, while vibration and position sense had normalized.

DISCUSSION

This case highlights possible diagnostic pitfalls in patients presenting with subacute ascending sensory disturbances and demyelinating neuropathy. First it shows that history taking and laboratory work-up with holotranscobalamin (or total cobalamin) alone can be misleading. Second, it underlines the importance of detailed and repeated drug history taking including asking for supplementary substances, especially if diagnostic tests are suggestive of a malnutrition-related disorder. In this case, holotranscobalamin levels were probably almost back to normal due to cobalamin supplementation initiated few days before hospitalization. However, strongly elevated blood levels of MMA and homocysteine proofed the ongoing metabolic deficiency and the decrease of MMA and homocysteine levels under appropriate supplementation with cyanocobalamin further supported this diagnosis (see [3] for a detailed review). Thus, this case emphasizes the assessment of metabolites of cobalamin including MMA and homocysteine to increase sensitivity for cobalamin deficiency, especially since total cobalamin and holotranscobalamin levels may still be normal or borderline normal while increased metabolites (MMA, homocysteine) already indicate cobalamin deficiency [4 5]. With only 0.1% of a middle-aged control group having MMA concentrations above 750nmol/l [6], a positive MMA just by chance seems very unlikely in our patient. Especially, as it was accompanied by severe homocysteine elevation in the presence of normal folate levels also strongly suggesting vitamin B12 deficiency. Upper gastrointestinal endoscopy belongs to the standard diagnostic work-up in patients with cobalamin deficiency to identify those cases with autoimmune or helicobacter pylori-associated gastritis and distinguish them from those with malnutrition or other causes of gastrointestinal malabsorption such as gluten-induced enteropathy, gastric bypass surgery or chronic alcohol ingestion. In our patient, however, the isolated duodenal ulcera with negative anti-intrinsic factor antibodies may not be sufficient to link cobalamin deficiency with gastrointestinal malabsorption. Also, long term-use of acid-suppressing medication (proton pump inhibitors and histamine 2 receptor antagonists) needs to be considered as an underlying cause of vitamin B12 malabsorption. Gastric acid is essential to cleave vitamins from nutritional proteins and intrinsic factor, which is required for

absorption of vitamin B12 in the ileum, is produced by the same cells that produce gastric acid [7].

With regards to the differential diagnosis, a distinction from acute inflammatory demyelinating polyneuropathy is essential – especially due the very recent symptom onset (about 2 weeks ago). However, both lack of cytoalbuminologic dissociation and preserved deep tendon reflexes speak against an inflammatory cause of the polyneuropathy. While the majority of cobalamin deficiency associated polyneuropathies is axonal or combined axonal-demyelinating, about 10-25% are purely demyelinating [8 9]. This may make distinction from an inflammatory cause of the neuropathy more difficult, especially, if symptom onset is very recent. Importantly, possible spinal cord involvement has to be addressed if clinical findings are not satisfactory explained by peripheral neuropathy. T2-hyperintensive myelopathy on MRI being most prominent at the posterior columns accompanied by clinical signs of damage of the posterior columns (impaired position-/ vibration-sense, decreased touch) is characteristic of subacute combined degeneration [10 11] and must initiate an intense search for cobalamin deficiency, while the clinician must be aware of the differential diagnosis including syphilitic myelopathy (tabes dorsalis) and copper deficiency (if cobalamin metabolites are normal) [12]. To our knowledge no similar cases with almost normal holotranscobalamin levels but severe MMA increases due to short-term supplementation have been published in the literature.

The pulmonary embolism found in our patient is possibly linked to the cobalamin deficiency also as high homocysteine levels were associated with an increased risk for venous thrombosis [13].

LEARNING POINTS/ TAKE HOME MESSAGES

- While acute / subacute ascending sensory deficits must initiate an urgent diagnostic work-up for acute inflammatory demyelinating polyneuropathy, normal protein levels and cell count on spinal tab, preserved deep tendon reflexes and electroneurographic measurements falling short of explaining all sensory deficits sufficiently make this diagnosis unlikely, shifting the focus on metabolic-toxic and malnutrition-related neuropathies that can have combined spinal and peripheral nerve involvement.
- Laboratory work-up for the evaluation of possible cobalamin deficiency should include holotranscobalamin, homocysteine and MMA, since a single parameter – holotranscobalamin in this case – may be almost normal despite severe deficiency as indicated by very high MMA serum and homocysteine levels.
- Drug history, especially long-term use of acid-suppressing medication, is essential for evaluation of vitamin B12-deficiency. We strongly recommend routinely evaluating for the intake of supplementary substances including vitamins as well.
- Prompt cobalamin supplementation and regular monitoring of cobalamin metabolites under supplementation are essential, as cobalamin-induced (neurological) deficits are potentially reversible if treated early.

REFERENCES

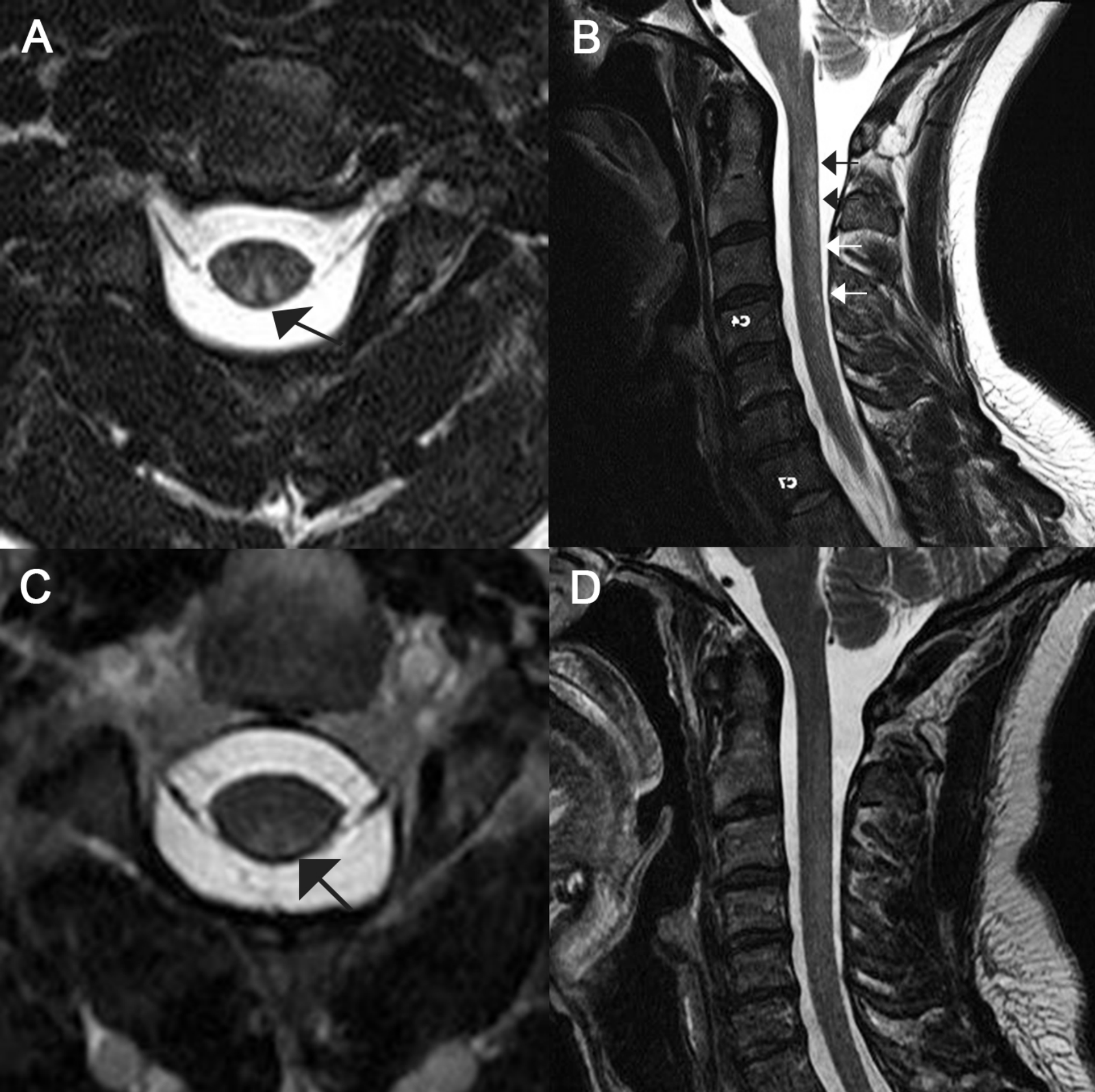
1. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barre syndrome: pathogenesis, diagnosis, treatment and prognosis. Nature reviews. Neurology 2014;**10**(8):469-82.
2. Vasconcelos OM, Poehm EH, McCarter RJ, Campbell WW, Quezado ZM. Potential outcome factors in subacute combined degeneration: review of observational studies. Journal of general internal medicine 2006;**21**(10):1063-8.
3. Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients 2013;**5**(11):4521-39.
4. Antony AC. Megaloblastic Anemias. In: Hoffman R, Benz EJ, Jr., Shattil SJ, eds. Hematology: Basic Principles and Practice, 5th ed. Philadelphia, PA: Elsevier Churchill Livingstone, 2009:473-504.
5. Saperstein DS, Wolfe GI, Gronseth GS, et al. Challenges in the identification of cobalamin-deficiency polyneuropathy. Archives of neurology 2003;**60**(9):1296-301.
6. Carmel R. Biomarkers of cobalamin (vitamin B-12) status in the epidemiologic setting: a critical overview of context, applications, and performance characteristics of cobalamin, methylmalonic acid, and holotranscobalamin II. The American journal of clinical nutrition 2011;**94**(1):348S-58S.
7. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA 2013;**310**(22):2435-42.
8. Kalita J, Chandra S, Bhoi SK, et al. Clinical, nerve conduction and nerve biopsy study in vitamin B12 deficiency neurological syndrome with a short-term follow-up. Nutritional neuroscience 2014;**17**(4):156-63.
9. Puri V, Chaudhry N, Goel S, Gulati P, Nehru R, Chowdhury D. Vitamin B12 deficiency: a clinical and electrophysiological profile. Electromyography and clinical neurophysiology 2005;**45**(5):273-84.
10. Hemmer B, Glocker FX, Schumacher M, Deuschl G, Lucking CH. Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. Journal of neurology, neurosurgery, and psychiatry 1998;**65**(6):822-7.
11. Russell JSR, Batten FE, Collier J. Subacute combined degeneration of the spinal cord. Brain : a journal of neurology 1900;**23**:39-110.
12. Jaiser SR, Winston GP. Copper deficiency myelopathy. Journal of neurology 2010;**257**(6):869-81.
13. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. Journal of thrombosis and haemostasis : JTH 2005;**3**(2):292-9.

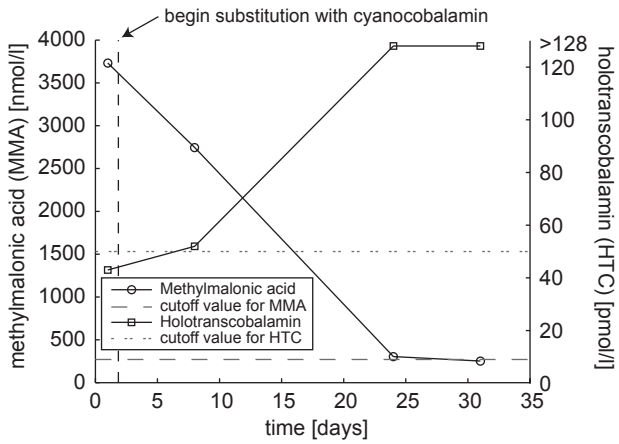
The patient was not involved in a clinical trial

FIGURE/ VIDEO CAPTIONS

Fig 1: Magnetic resonance imaging of the spinal cord before (panels A, B) and two months after (panels C, D) initiating cobalamin supplementation. T2-weighted axial (panels A, C) and sagittal (panels B, D) cuts are presented, demonstrating marked T2-hyperintensity along the posterior columns of the cervical spinal cord (as indicated by the black and white arrows) in axial and sagittal sections, referred to as subacute combined degeneration. On follow-up, these changes were markedly reduced (panel C) or have even disappeared (panel D).

Fig 2: Methylmalonic acid (black circles) and holotranscobalamin (black squares) levels before and during the first month of supplementation with cyanocobalamin relative to cutoff values for MMA (normal range < 271 nmol/l) and cyanocobalamin (normal range > 50 pmol/l).


A
B
C4
C5
C
D


begin substitution with cyanocobalamin
methylmalonic acid (MMA) [nmol/l]
holotranscobalamin (HTC) [pmol/l]
time [days]
Methylmalonic acid
cutoff value for MMA
Holotranscobalamin
cutoff value for HTC
4000
3500
3000
2500
2000
1500
1000
500
0
>128
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35